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Candida glabrata fungaemia in intensive care units

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ABSTRACT

Candidaemia is increasingly important in intensive care units (ICUs). Compared with *Candida albicans* fungaemia, the impact of *C. glabrata* fungaemia on ICU patients is not well-known. The aim of this study was to investigate the clinical features, the antifungal susceptibility and the treatment outcomes of *C. glabrata* fungaemia in ICU patients. The medical records of ICU patients with candidaemia between 2000 and 2005 were reviewed retrospectively, and antifungal susceptibility testing was performed for isolates of *C. glabrata*. Among 147 episodes of candidaemia occurring in adult ICUs, *C. glabrata* was the second most common species and accounted for 45 (30%) episodes of candidaemia. The incidence of *C. glabrata* fungaemia was 1.3/1000 ICU admissions. Fluconazole resistance was found in 11% of *C. glabrata* isolates. The 30-day all-cause mortality rate was 58%. Therapeutic regimens containing amphotericin B were associated with better outcome. Despite higher fluconazole resistance, *C. glabrata* candidaemia was not associated with greater mortality than non-*glabrata* candidaemia in the ICU setting.

Keywords *Candida glabrata*, epidemiology, fungaemia, intensive care units, mortality, treatment outcome

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INTRODUCTION

Bloodstream infection caused by *Candida* spp. is increasingly important in critical care [1]. In the USA, *Candida* spp. are the third most common cause of nosocomial bloodstream infection in intensive care units (ICUs), and are associated with high mortality [1]. The proportion of non-*albicans Candida* spp. causing candidaemia has increased during recent decades, and it is considered that frequent use of fluconazole has played a major role in this increase [2–4]. Of the non-*albicans Candida* spp., *Candida glabrata* has emerged as an important cause of fungaemia in the ICU [4]. *C. glabrata* has unique biological and genetic characteristics compared with other *Candida* spp., in that it is smaller in morphology, cannot form pseudohyphae, and has a haploid rather than a diploid genome [5,6].

Despite these differences between *C. albicans* and other *Candida* spp., the question of whether *C. glabrata* fungaemia differs in clinical features and outcome from fungaemia caused by other *Candida* spp. remains unclear. Although several studies have examined the epidemiology or outcome of candidaemia in the ICU setting, data focused on *C. glabrata* are limited [2,4,7–9]. The present study retrospectively reviewed the clinical features and treatment outcomes of *C. glabrata* fungaemia occurring in ICU patients during 2000–2005 in our hospital. Antifungal susceptibility testing of *C. glabrata* isolates was also performed.

MATERIALS AND METHODS

Patients

All patients with *Candida* bloodstream infection between January 2000 and December 2005 were identified from the records of the microbiology laboratory at National Taiwan University Hospital, a tertiary-care medical centre in Taiwan. Episodes of candidaemia developing >48 h after ICU admission were considered to have occurred in the ICU and were included in the analysis. Episodes of candidaemia that occurred in patients in the paediatric ICU were excluded. An episode of *C. glabrata* fungaemia was recorded when at least one blood culture was positive for *C. glabrata*. Fungaemia occurring in the same patient during the same hospital admission period was counted as only one episode. Medical records were reviewed retrospectively to collect data

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concerning demographical characteristics, treatment and outcome. Predisposing factors reported previously to be associated with candidaemia were recorded [10].

Antifungal susceptibility testing

C. glabrata isolates were stored in the mycology laboratory at −70°C in trypticase soy broth containing glycerol 15% v/v. Before susceptibility testing, the isolates were passaged twice on potato dextrose agar. Antifungal susceptibility testing was performed using the reference broth microdilution method according to CLSI guidelines [11]. The tested concentrations of antifungal agents ranged from 0.03 to 64 mg/L. Two reference strains, *Candida parapsilosis* ATCC 22019 and *Candida krusei* ATCC 6258, were used as quality control strains. MICs were determined after incubation for 48 h. Antifungal susceptibilities were interpreted according to CLSI guidelines and other recommendations [10,11].

Statistical analyses

Categorical variables were assessed using Fisher's exact test or chi-square tests, as appropriate, while the probability of survival was estimated using the Kaplan–Meier method; p values <0.05 were considered to be statistically significant.

RESULTS

Epidemiological and clinical features

During the 6-year period from January 2000 to December 2005, there were 147 episodes of candidaemia in the adult ICUs of the hospital, and these accounted for 27% of the total episodes of candidaemia in the hospital. Among the episodes of ICU candidaemia, *C. glabrata* was the second most common causative species, and accounted for 30% of episodes (Table 1). The incidence of candidaemia in ICUs during the study period was 4.3/1000 ICU admissions, or 5.9/10 000 patient-days. For *C. glabrata* fungaemia, the incidence was 1.3/1000 ICU admissions. The incidence trends are shown in Fig. 1. The incidence of *C. glabrata* fungaemia in the ICUs ranged from 0.59 to 2.17/1000 ICU admissions, and peaked during 2003.

The clinical features of cases of *C. glabrata* fungaemia in ICUs are summarised in Table 2.

Table 1. Species distribution of 147 episodes of candidaemia occurring in adult intensive care units

Species	Number of episodes (%)
Candida albicans	57 (39)
Candida glabrata	45 (30)
Candida tropicalis	26 (18)
Candida parapsilosis	12 (8)
Candida guilliermondii	3 (2)
Others	4 (3)

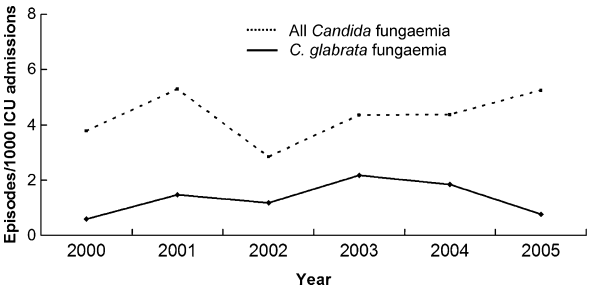

Fig. 1. Incidence of candidaemia and *Candida glabrata* fungaemia in adult intensive care units (ICUs).

Table 2. Characteristics of 45 episodes of *Candida glabrata* fungaemia in adult intensive care units (ICUs)

Characteristic	Value
Age (mean years ± SD)	70 ± 14
Gender, male/female	24(53%)/21(47%)
APACHE II score at ICU admission (mean ± SD)	24.3 ± 8.7
ICU specialty, medical/surgical	28 (62%)/17(38%)
Onset of fungaemia: median hospital days	32
Median ICU days	13
Organ failure or systemic diseases (%)	
Respiratory failure with mechanical ventilation	93
Renal failure requiring dialysis	53
Hepatic dysfunction[a]	20
Malignancy	31
Autoimmune disease	11
Diabetes	38
Risk-factors (%)	
Previous antimicrobial use[b]	98
Previous fluconazole use[b]	31
Chemotherapy[b]	11
Systemic steroids[b]	29
Neutropenia[c]	2
Receipt of parenteral nutrition	53
Intravascular devices	96
Previous abdominal surgery	36

APACHE, acute physiology and chronic health evaluation score.
[a]Class B or C in Child–Pugh classification.
[b]Receipt of antibiotics, fluconazole, chemotherapy or systemic steroids during the previous 30 days.
[c]<500 neutrophils/mm^3 for >48 h during the previous 7 days.

Most of the patients who developed *C. glabrata* fungaemia in an ICU had multiple underlying illnesses (Table 2). On average, each patient experienced failure of 2.5 organs. In addition to underlying disease, common risk-factors included previous use of antimicrobial agents, intravascular devices, parenteral nutrition, previous abdominal surgery and previous fluconazole exposure.

Antifungal susceptibilities

Overall, 60% of *C. glabrata* isolates were susceptible to fluconazole (MIC ≤8 mg/L), 29% were susceptible/dose-dependent (MIC 16–32 mg/L), and 11% were resistant to fluconazole (MIC >32 mg/L). However, there was no associ-

ation between the presence or absence of fluconazole resistance and 30-day mortality (p 0.113). Amphotericin B and caspofungin were highly active against *C. glabrata* (100% susceptible), with MICs of ≤1mg/L and ≤2 mg/L, respectively.

Treatment and outcome

Forty of 45 episodes of *C. glabrata* fungaemia were treated with various regimens of antifungal agents. Of the five untreated episodes, four involved death of the patient before diagnosis, and one patient was treated only by removal of a central venous catheter. Among the 40 treated episodes, antifungal agents were initiated at a mean of 2 days after blood culture was performed, with 26 (65%) of 40 patients receiving antifungal therapy within 48 h. The treatment regimens and outcomes are listed in Table 3. Fluconazole was the initial antifungal agent used in 97.5% of episodes. The most common treatment regimen, used in 52.5% of episodes, comprised initial treatment with fluconazole followed by a switch to amphotericin B after identification of the infecting species as *C. glabrata*. Fluconazole alone was used in 40% of episodes. Amphotericin B-containing regimens, used in 55% of episodes, were associated with lower mortality than were regimens without amphotericin B (p 0.048, chi-square test). The 30-day all-cause mortality rate was 58%. Fig. 2 compares the survival of patients with fungaemia caused by *C. glabrata* and that caused by other *Candida* spp.; there was no significant difference in survival between the two groups (p 0.688, log-rank test).

DISCUSSION

Candidaemia is an important nosocomial bloodstream infection among ICU patients [9,10].

Table 3. Treatment regimens for *Candida glabrata* fungaemia in adult intensive care units and 30-day all-cause mortality rate

Treatment regimens (treated episodes, *n* = 40)	Episodes of fungaemia, *n* (%)	Deaths within 30 days, *n* (%)
Fluconazole alone	16 (40)	11
Fluconazole followed by amphotericin B	21 (52.5)	9
Fluconazole followed by caspofungin	2 (5)	2
Caspofungin followed by amphotericin B	1 (2.5)	0
Regimens without amphotericin B	18 (45)	13 (72)[a]
Regimens containing amphotericin B	22 (55)	9 (41)[a]

[a]p 0.048 (chi-square test).

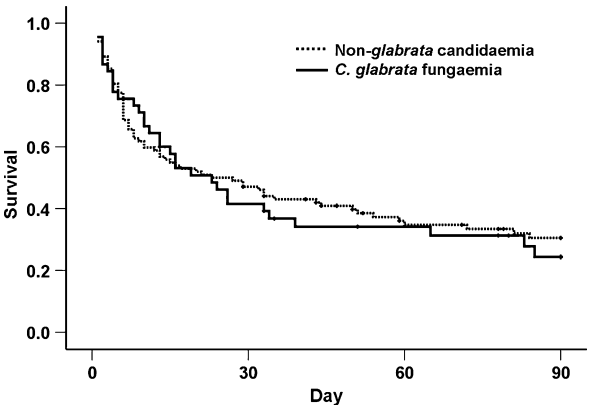

Fig. 2. Overall survival of patients in adult intensive care units with *Candida glabrata* fungaemia (*n* = 45) and fungaemia caused by other *Candida* spp. (*n* = 102).

C. glabrata has accounted for 10–30% of cases of candidaemia in ICUs in various reports, and an increasing incidence has been noted in some areas [4,7,12]. In the present study, *C. glabrata* was the second most common cause of candidaemia and accounted for 30% of the episodes of candidaemia in adult ICUs. The annual incidence of *C. glabrata* fungaemia varied during the study period (Fig. 1) and, in contrast to a previous study [4], a continuously increasing incidence of *C. glabrata* fungaemia in ICUs was not observed. It is not clear why the incidence of *C. glabrata* fungaemia peaked in 2003 and then declined between 2003 and 2005. However, consumption of fluconazole in the hospital also peaked in 2003 and decreased in the following 2 years (data not shown).

Several previous studies have thoroughly investigated the risk-factors associated with invasive candidiasis and candidaemia [9,10]. Susceptible hosts and existing portals of entry are two major risk-factors for developing candidaemia. The disease patterns and risk-factors associated previously with candidaemia [10] were also commonly seen in the patients with *C. glabrata* fungaemia (Table 2). Most of the patients had multiple organ dysfunction and, because of the ICU setting of this study, the proportion of patients with respiratory failure was also high. However, the proportions of patients on dialysis (53%) and with malignancy (31%) were higher than would be expected among ICU patients; a possible explanation could be the existence of a suitable portal of entry. The gut and the skin are thought to be the two major portals of entry, and the latter has been implicated in the pathogenesis of catheter-related

candidaemia [13]. In the present study, more than half of the patients with malignancy suffered from cancer of the gastrointestinal tract, and these patients often had long-term central catheters (Port-A cath or double lumen catheter). The underlying diseases and risk-factors found in a high percentage of patients (Table 2) reflect a picture of immunocompromised hosts with suitable portals of entry. Exposure to fluconazole had occurred in 31% of cases, and exposure to azoles has been considered to contribute to species shift to non-*albicans Candida* spp. in many previous studies [3,14,15].

Compared with *Candida albicans*, *C. glabrata* has been found to be relatively resistant to azole antifungal agents [16–18]. However, it remains to be clearly established whether bloodstream isolates from ICU patients are associated with higher azole resistance. In the present study of ICU patients, 11% of bloodstream isolates were resistant to fluconazole, which is similar to the figure of 14% revealed by a national antifungal resistance surveillance study in Taiwan in which *C. glabrata* isolates were not restricted to ICU patients [19]. Caspofungin and amphotericin B still remained highly active against the *C. glabrata* isolates from ICU patients in the present study.

Fluconazole resistance is a great concern in the management of patients with *C. glabrata* candidaemia, particularly as prompt susceptibility testing is not always available. Fluconazole and amphotericin B were considered to have similar treatment outcomes in several previous studies of non-neutropenic patients with candidaemia [20–22]. However, this finding cannot be generalised to all patients, especially critically-ill ICU patients, and these studies focused mainly on *C. albicans* candidaemia. One study has reported similar mortality rates among patients with *C. glabrata* candidaemia who received fluconazole rather than other antifungal therapy, but this study included all hospitalised patients in the analysis [23]. In the present study, all of the patients were hospitalised in the ICU, and amphotericin B-containing regimens were revealed to be associated with significantly lower mortality. The Infectious Diseases Society of America (IDSA) has suggested treating serious cases of *C. glabrata* candidaemia with amphotericin B or caspofungin, rather than with fluconazole [24,25]. The differences in study designs (retrospective without selection in the present study, as compared with prospective in a selected population of patients in the randomised trials) also contribute to different outcomes.

The outcome of ICU patients with candidaemia is poor, with mortality ranging from 47% to 58% in previous studies [1,10]. Despite this well-established impact of candidaemia on ICU mortality, data concerning the impact of *C. glabrata* candidaemia on ICU patients are scarce. In theory, *C. glabrata* has higher resistance to azoles, and may therefore be associated with higher mortality as compared with non-*glabrata* candidaemia. However, a previous study reported that the mortality rates were similar among patients with *C. glabrata* or non-*glabrata* candidaemia, although this previous study was not focused specifically on ICU patients [23]. In the present study, the all-cause 30-day mortality rate of ICU patients with *C. glabrata* fungaemia was 58%. No significant difference between the survival of patients with *C. glabrata* and those with non-*glabrata* candidaemia in ICUs was found, with *C. glabrata* and non-*glabrata* candidaemia having a similar impact on 30-day survival rates.

The present study had several limitations. First, the ICU patients were critically-ill, and many factors contributed to their death. It was difficult to clarify the contribution of fungaemia to mortality, and all-cause mortality was therefore chosen, rather than fungaemia-related death, for outcome analyses. However, the choice of 30 days for the mortality analysis was arbitrary. Second, the choice of antifungal agent did not follow a consistent protocol during the study period, and depended mainly on the clinical judgement of the critical care specialists. Selection biases were prominent problems. Third, because of the retrospective design of this study, it was not possible to obtain the APACHE II score at the time of onset of fungaemia, and therefore it was not possible to adjust for the influence of underlying disease.

In conclusion, this study confirmed that *C. glabrata* and non-*glabrata* candidaemia resulted in similar outcomes among ICU patients, despite the differences in biology, antifungal susceptibilities and genetics of these two groups of organisms.

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